REMARKS

Claims 32-47 were pending before this Response. By the present communication, claims 32, 33 and 43 through 47 have been amended as shown in attached Exhibit A to define Applicant's invention with greater particularity. The amendments add no new matter, being fully supported by the specification and original claims. Applicant submits that the claim amendments do not narrow the claims in any way within the meaning of Festo Corporation v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd., a/k/a SMC Corporation and SMC Pneumatics, Inc. 234 F.3d 558, 51 U.S.P.Q. 2d 1959 (Fed. Cir. 2000). Accordingly claims 32-47 are presently pending.

The Declaration

The Office Action asserts that a new oath or declaration is required in compliance with 37 C.F.R. 1.67(a) containing the claimed priority information. In compliance with this request, Applicant submits herewith a new unsigned declaration that claims the benefit under 35 U.S.C. §120 of the U.S. patent applications listed in the replacement paragraph submitted herewith for entry as paragraph 1 of page 1. A similar new declaration containing signatures of the co-inventors herein will be submitted as soon as their signatures have been obtained. Thus, Applicant respectfully submits that the new declaration submitted herewith contains the priority information consistent with the first paragraph of the specification as amended herein and meets all requirements under 37 C.F.R. 1.67(a). Accordingly, withdrawal of the objection to the declaration is respectfully requested.

The Drawings

The Office Action raises and objection to the drawings due to defects noted on the attached PTO-498. In response to this objection, Applicant respectfully submits that corrected drawings will be submitted upon notification of allowable subject matter in this application. Accordingly, withdrawal of the objection to the drawings is respectfully requested.

The Objection to the Specification and Rejection under 35 U.S.C. 112, First Paragraph

Claims 32-47 are rejected under 35 U.S.C. §112, First Paragraph, as being based on a Specification that allegedly lacks a sufficient written description for the invention as claimed. The Examiner asserts that claims 32-47, which encompass gene clusters of metabolic pathways, are "not enabled in parent applications serial numbers 08/503,606, and 08/568,994 from which serial number 08/988,224 is a continuation in part. Since claims 32-33 and 36-47 are not limited to specified enzymatic activities, the claims encompass gene clusters of metabolic pathway which have the priority date of June 3, 1996" (Office Action, page 2). However, Applicant submits that the disclosure in the present Specification is not limited to gene clusters that encode enzymatic activities. In fact, in the present specification, gene clusters encoding enzymes are merely exemplary of gene clusters encoding metabolic pathways in general (See Specification, page 3, lines 5-20 and page 4, line 11 to page 6, line 1).

In addition, the new Declaration submitted herewith additionally claims priority from pending U.S. Patent Application Serial No. 09/089,789, filed June 3, 1998, which is a continuation-in-part application of U.S. Patent Application Serial No.09/034,724, filed March 4, 1998, now issued as U.S. Patent No. 6,001,574; which is a continuation in part application of U.S. Patent Application Serial No. 08/665,565, filed June 18, 1996, now issued as U. S. Patent No. 5,763,239, each of which is incorporated into the present application by reference in its entirety. It is respectfully submitted that these newly cited priority documents provide additional enablement for gene clusters of metabolic pathways in general, and not just for those that encode enzymatic activities. Accordingly, Applicant respectfully submits that the Specification and priority documents provide enablement under 35 U.S.C. § 112, First Paragraph, for pending claims 32-47.

The Double Patenting Rejection

Applicant traverses the rejection and provisional rejection of claims 32-47 under the judicially created doctrine of obviousness-type double patenting as being unpatentable as follows:

In traversal of the rejection over claims 1-15 of U.S. Patent No. 5,958,672, Applicant submits herewith a Terminal Disclaimer disclaiming the terminal part of any patent granted on claims 32-47 of the above-identified Application No. 09/421,629 that would extend beyond the

expiration date of U.S. Patent No. 5,958,672. In addition, Applicant submits that Diversa Corporation, Inc. commonly owned the subject matter of Application No. 09/421,629 and of U.S. Patent No. 5,958,672 at the filing date of the present application.

In traversal of the rejection over claims 1-15 of U.S. Patent No. 6,168,919, Applicant submits herewith a Terminal Disclaimer disclaiming the terminal part of any patent granted on claims 32-47 of the above-identified Application No. 09/421,629 that would extend beyond the expiration date of claims 1-15 of U.S. Patent No. 6,168,919. In addition, Applicant submits that Diversa Corporation, Inc. commonly owned the subject matter of Application No. 09/421,629 and of U.S. Patent No. 6,168,919 at the filing date of the present application.

In traversal of the rejection over claims 1-23 of U.S. Patent No.6,174,673, Applicant submits herewith a Terminal Disclaimer disclaiming the terminal part of any patent granted on claims 32-47 of the above-identified Application No. 09/421,629 that would extend beyond the expiration date of claims 1-23 of U.S. Patent No. 6,174,673. In addition, Applicant submits that Diversa Corporation, Inc. commonly owned the subject matter of Application No. 09/421,629 and of U.S. Patent No. 6,174,673 at the filing date of the present application.

In traversal of the provisional rejection over allowed claims 66-71 and 74-85, 89, 90, 92 and 93 of copending Application No. 08/988,224, Applicant submits herewith a Terminal Disclaimer disclaiming the terminal part of any patent granted on claims 32-47 of the above-identified Application No. 09/421,629 that would extend beyond the expiration date of any

patent granted on claims 66-71, 74-85, 89, 90, 92 and 92 of copending Application No. 08/988,224. In addition, Applicant submits that Diversa Corporation, Inc. commonly owned the subject matter of Application No. 09/421,629 and of Application No. 08/988,224 at the filing date of the present application.

In traversal of the provisional rejection over allowed claims 2-5 of copending Application No. 09/467,740, Applicant submits herewith a Terminal Disclaimer disclaiming the terminal part of any patent granted on claims 32-47 of the above-identified Application No. 09/421,629 that would extend beyond the expiration date of any patent granted on claims 2-5 of copending Application No. 09/467,740. Applicant submits that the subject matter of Application No. 09/421,629 and of Application No. 09/467,740 was commonly owned by Diversa Corporation, Inc. at the filing date of the present application.

Applicant respectfully submits that the Terminal Disclaimer and above remarks overcome the actual and provisional rejections based on obviousness-type double patenting over claims 1-15 of U.S. Patent No. 5,958,672; claims 1-15 of U.S. Patent No. 6,168,919; claims 1-23 of U.S. Patent No. 6,174,673; claims 66-71; and 74-85,89, 90, 92 and 92 of copending Application No. 08/988,224; and claims 2-5 of copending Application No. 09,467,740. Accordingly, reconsideration and withdrawal of the rejection for obviousness-type double patenting are respectfully requested.

The Rejection Under 35 U.S.C. §112, Second Paragraph

Applicant traverses the rejection of claims 32-47 under 35 U.S.C. §112, Second Paragraph, for allegedly being indefinite. With regard to the Examiner's assertion that the phrase "DNA so isolated" in claims 32 and 44 renders the claims indefinite, claims 32 and 44 have been amended to replace the phrase "DNA so isolated." As presently claimed, step a) of the invention method requires (i) amplifying the copy number of the cDNA or genomic DNA fragments or (ii) amplifying the copy number of at least a portion of the cDNA or genomic DNA fragments." A similar corresponding amendments have been made in claim 43 to delete "isolated" and in claim 44 to replace the phrase "DNA so isolated," thus clarifying the alternate procedures claimed for forming the initial (i.e., prior to normalization) library.

With regard to the Examiner's assertion that the phrase "in the normalized library" in the final line of claim 32 lacks clarity, Applicant respectfully submits that claim 32 has been amended to emphasize that in step a) a library is formed by one of two steps plus normalization of the library to form a normalized library, and in step b) a bioactivity or biomolecule of interest encoded by DNA in the normalized library identified. Applicant respectfully submits that these amendments to claim 32 clarify that the normalized library is screened for a bioactivity or biomolecule of interest.

With regard to the Examiner's assertion that the phrase "the process of claim 32" allegedly renders claims 45-47 indefinite, Applicant has amended claims 45-47 to replace

"process" with "method" in agreement with claim 32, thus clarifying the dependency of claims 45-47 and overcoming the ground of the rejection.

In view of the above amendments and remarks, Applicant respectfully submits that amended claims 32-47 meet all requirements of definiteness under 35 U.S.C. §112, Second Paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 102(e)

Applicant traverses the rejection of claims 32 and 36-44 as allegedly being anticipated under 35 U.S.C. §102(e) by Thompson et al. (U.S. Patent No. 5,824,485; hereinafter "Thompson"). Applicant respectfully submits that the invention methods for identifying a bioactivity or biomolecule of interest, as defined by amended claim 32, distinguish over the methods disclosed by Thompson at least by requiring a) formation of a library by amplification of all or a portion of a group of vectors containing cDNA or genomic DNA fragments and normalizing the representation of various DNAs within the cDNA or genomic DNA fragments so as to form a normalized library of cDNA or genomic DNA fragments; and b) identifying the bioactivity or biomolecule of interest encoded by the cDNA or genomic DNA fragments in the normalized library.

Applicant respectfully submits that Thompson is absolutely silent regarding normalizing the representation of various DNAs within a group of vectors containing cDNA or genomic

DNA fragments prior to screening to identify a bioactivity or biomolecule of interest encoded by the fragments in the normalized library. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir., 1990). Since Thompson at least fails to disclose methods for normalizing the representation of various DNAs contained within an amplified library, Applicant respectfully submits that Thompson does not support a rejection for alleged anticipation under 35 U.S.C. § 102(e). Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

In view of the above amendments and remarks, reconsideration and favorable action on claims 32-47 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call Applicant's representative at (858) 677-1456 so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: **November 14, 2001**

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

USPTO CUSTOMER NO. 28213

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

Attachment: Exhibit A

Gray Cary\GT\6255808.1
104703-158574

Gray Cary\GT\6255808.1
104703-158574

Applicant: Short, et al.
Serial No.: 09/421,629
Filed: October 19, 1999
Exhibit A: Page 1

Art Unit: 1652
Examiner: N. Nashed

EXHIBIT A
MARKED-UP VERSION OF THE AMENDMENTS

Please delete Paragraph 1 on page 1 and replace it with the following substitute paragraph:

-- This application is a continuation application of U.S. Patent Application Serial No. 08/657,409, which was filed on June 3, 1996, now issued as U.S. Patent 5,958,672; which was a continuation-in-part of U.S. application Serial No. 08/568,994 which was filed on December 7, 1995, now abandoned; which is a continuation-in-part of U.S. application Serial No. 08/503,606 which was filed on July 18, 1995, now issued as U.S. Patent 6,004,788; and a continuation application of U.S. Patent Application Serial No. 09/089,789, filed June 3, 1998, pending; which is a continuation-in-part application of U.S. Patent Application Serial No.09/034,724, filed March 4, 1998, now issued as U.S. Patent No. 6,001,574; which is a continuation in part application of U.S. Patent Application Serial No. 08/665,565, filed June 18, 1996, now issued as U. S. Patent No. 5,763,239, each of which is incorporated herein by reference in its entirety. --

Please amend the paragraph beginning at line 5 of page 3 as follows:

--The invention also provides a process of screening clones having DNA from an uncultivated microorganisms for a specified protein, e.g [en~yme] <u>enzyme</u>, activity which comprises screening for a specified gene cluster protein product activity in the library of clones prepared by: (i) recovering DNA from a DNA population derived from at least one uncultivated microorganism; and (ii[3] transforming a host with recovered DNA to produce a library of clones with the screens for the specified protein, e.g enzyme, activity. The library is produced from gene cluster DNA which is recovered without culturing of an organism, particularly where the

Applicant: Short, et al.
Serial No.: 09/421,629
Filed: October 19, 1999
Exhibit A: Page 2

DNA gene clusters are recovered from an [envirorunental] environmental sample containing microorganisms which are not or cannot be cultured.

Please amend the paragraph beginning at line 25 of page 3 as follows:

The microorganisms from which the libraries may be prepared include prokaryotic microorganisms, such as Eubacteria and [Archacbacteria] Archeabacteria, and lower eukaryotic microorganisms such as fungi, some algae and protozoa. The microorganisms are uncultured microorganisms obtained from environmental samples and such microorganisms may be extremophiles, such as thermophiles, hypertherrnophiles, psychrophiles, psychrotrophs, etc.

Please amend the paragraph beginning at line 8 of page 5 as follows:

Polyketides are molecules which are an extremely rich source of bioactivities, including antibiotics (such as tetracyclines and erythromycin), anti-cancer agents (daunomycin), immunosuppressants (FK506 and rapamycin), and veterinary products (monensin). Many polyketides (produced by polyketide syntheses) are valuable as therapeutic agents. Polyketide syntheses are multifunctional proteins, e.g. enzymes, that catalyze the biosynthesis of a hugh variety of carbon chains differing in length and patterns of functionality and cyclization. Polyketide synthase genes fall into gene clusters and at least one type (designated type I) of polyketide syntheses have large size genes and proteins, e.g. enzymes, complicating genetic manipulation and in [v'ro] vitro studies of these genes/proteins.

Applicant: Short, et al.
Serial No : 09/421,629
Filed: October 19, 1999
Exhibit A: Page 3

Please amend the paragraph beginning at line 24 of page 5 as follows:

Preferably, the gene cluster DNA is ligated into a vector, particularly wherein a vector further comprises expression regulatory sequences which can control and regulate the production of a detectable protein or protein-related array activity from the ligated gene clusters. Use of vectors which have an exceptionally large capacity for exogenous DNA introduction are particularly appropriate for use with such gene clusters and are described by way of example herein to include the f-factor (or fertility factor) of E. coli. This f-factor of E. [cold] coli is a plasmid which affect [highfrequency] high frequency transfer of itself during conjugation and is ideal to achieve and stably propagate large DNA fragments, such as gene clusters [frorr.] from mixed microbial samples.

Applicant: Jay M. Short
Serial No.: 09/421,629
Filed: October 19, 1999
Exhibit A: Page 4

Please amend the paragraph beginning at line 17 of page 6 as follows:

The following outlines a general procedure for producing libraries from nonculturable organisms, which libraries can be probed to select therefrom DNA sequences which hybridize to specified probe DNA:

Obtain Biomass

DNA Isolation

Shear DNA (25 gauge needle)

Blunt DNA (Mung Bean Nuclease)

Methylate (EcoR I Methylase)

Ligate to EcoR I linkers (GGAATTCC)

Cut back linkers (EcoR I Restriction Endonuclease)

Size Fractionate (Sucrose Gradient)

Ligate to lambda vector (Lambda ZAP7 (Stratagene) and gtl1)

Package (in vitro lambda packaging extract)

Plate on E. [cold] coli host and amplify

Applicant: Jay M. Short
Serial No.: 09/421,629
Filed: October 19, 1999
Exhibit A: Page 5

Please amend the paragraph beginning at line 1 of page 9 as follows:

The screening for protein, e.g. enzyme, activity may be effected on individual expression clones or may be initially effected on a mixture of expression clones to ascertain whether or not the mixture has one or more specified protein, e.g. enzyme, activities. If the mixture has a specified protein, e.g. [er~yme] enzyme, activity, then the individual clones may be rescreened for such protein, e.g. enzyme, activity or for a more specific activity. Thus, for example, if a clone mixture has hydrolase activity, then the individual clones may be recovered and screened to determine which of such clones has hydrolase activity.

Please amend the paragraph beginning at line 1 of page 10 as follows:

A particularly preferred type of vector for use in the present invention contains an f-factor origin of replication. The f-factor (or fertility factor) in E. coli is a plasmid which effects high frequency transfer of itself during conjugation and less frequent transfer of the bacterial chromosome itself. A particularly preferred embodiment is to use cloning vectors, referred to as "fosmids" or bacterial artificial chromosome (BAC) vectors. These are derived from the E. [cold] coli f-factor and are able to stably integrate large segments of genomic DNA. When integrated with DNA from a mixed uncultured environmental sample, this makes it possible to achieve large genomic fragments in the form of a stable "environmental DNA library."

Applicant: Jay M. Short
Serial No.: 09/421,629
Filed: October 19, 1999
Exhibit A: Page 6

Please amend the paragraph beginning at line 1 of page 11 as follows:

Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g, the ampicillin resistance gene of E. [cold] coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic proteins, e.g enzymes, such as 3-phosphoglycerate kinase (PGK), a-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium.

Applicant: Jay M. Short
Serial No.: 09/421,629
Filed: October 19, 1999
Exhibit A: Page 7

In the claims:

Please amend claims 32, 33 and 43 through 47 as follows:

32. (Amended) A method for identifying a [protein] bioactivity or biomolecule of interest comprising:

a) culturing a gene expression library comprising a pool of expression constructs, each expression construct comprising a vector containing one or more cDNA or genomic DNA fragments, wherein the cDNA or genomic DNA fragments in the pool of expression constructs are derived from a plurality of species of donor organisms[, and wherein the cDNA or genomic DNA fragments are operably-associated with one or more regulatory regions that drives expression of genes encoded by the cDNA or genomic DNA fragments in an appropriate host organism], wherein the library is formed by [performing at least one of the steps selected from the group consisting of (i) amplifying the copy number of the DNA population so isolated cDNA or genomic DNA fragments and (ii) amplifying the copy number of the DNA population so isolated at least a portion of the cDNA or genomic DNA fragments; and] normalizing the representation of various DNAs within the cDNA or genomic DNA [population] fragments so as to form a normalized library of cDNA or genomic DNA fragments; and

b) [detecting] identifying the [protein] bioactivity or biomolecule of interest encoded by the cDNA or genomic DNA fragments in the normalized library.

33. (Amended) The method of claim 32, wherein the [protein activity] bioactivity is an enzymatic activity.

Applicant: Jay M. Short
Serial No.: 09/421,629
Filed: October 19, 1999
Exhibit A: Page 8

43. (Amended) The method of claim 32, which comprises the step of recovering a fraction of the [isolated] DNA having a desired characteristic.

44. (Amended) The method of claim 32 which comprises the step of amplifying the copy number of the [DNA population so isolated] cDNA or genomic DNA fragments.

45. (Amended) The [process] method of claim 32 wherein the step of amplifying the DNA precedes the normalizing step.

46. (Amended) The [process] method of claim 32 wherein the step of normalizing the DNA precedes the amplifying step.

47. (Amended) The [process] method of claim 32 which comprises both the steps of (i) amplifying the copy number of the DNA population so isolated and (ii) recovering a fraction of the isolated DNA having a desired characteristic.